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Patients with dravet syndrome in the era of stiripentol: A French cohort cross-sectional study

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ABSTRACT

Objective: The aim of this study was to assess outcome and seizure response to treatment with stiripentol (STP) associated to valproate (VPA) and clobazam (CLB), which we have used in our center since the 1990s, in patients with Dravet syndrome (DS).
Methods: We performed a cross-sectional study of all DS patients with *SCN1A* mutations who had at least one visit to our center in 2013. A total of 54 patients were included (32 males, 22 females), whose ages ranged from 2.5 to 22 years.
Results: Seizure onset ranged from 2 to 9 months (mean 5 months). Treatment started at a mean age of 7 months with valproate (VPA) as first therapy in 83% of patients. STP was prescribed in 96% at an average age of 20 months. At last follow-up (up to 22 years, median 8 years), 96% were still receiving STP, with VPA and clobazam (CLB) in 91%. Additional therapies were prescribed in 72% of patients. Most patients (96%) continued to have clonic or tonic-clonic seizures but they were brief (<5 min, with last status epilepticus (SE) episode being before 4 years of age). Seizures occurred weekly (>3/month) in 38% of patients, monthly (1–3/month) in 40%, and yearly in the remaining patients. None presented with daily seizures. Seizure frequency at last visit was related to the age of treatment initiation, the age of last SE, and *SCN1A* mutation type.
Conclusions: Triple therapy with STP, VPA, and CLB was maintained long-term by 96% of this large DS cohort because the reduced frequency and severity of seizures STP provided when added to CLB and VPA was durable. Nevertheless, only a few patients achieved seizure freedom and persisting seizures remains a concern in the majority of patients.

1. Introduction

Dravet syndrome (DS) (OMIM 607208), is a serious, intractable epilepsy syndrome that is characterized by prolonged febrile and afebrile, often unilateral, tonic-clonic (TC) seizures beginning in the first year of life. Later, focal seizures, myoclonic jerks, and atypical absences may develop with TC seizures and susceptibility to fever. These seizures persist long-term, often life-long, and achieving seizure freedom is rarely reported (Takayama et al., 2014). Status epilepticus (SE) in DS patients is frequent during early childhood (Dravet and Oguni, 2013), despite the fact that electroencephalogram (EEG) readings are initially normal. From the second year of life onward, EEGs show the development of background slowing with focal spikes, generalized spikes, and polyspike waves (Dravet and Oguni, 2013). Psychomotor outcome is typically poor, manifesting with gait disorders, developmental delays,

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and behavioral problems (Dravet and Oguni, 2013; Nabbout et al., 2013). In the majority of DS patients (approximately 80%), DS is known to be caused by *SCN1A* mutations or deletions (Dravet and Oguni, 2013).

Although several antiepileptic drugs (AEDs) may be useful in DS patients, long-term benefit is poorly documented and seizure freedom remains elusive (Takayama et al., 2014).

Stiripentol (STP) was approved for DS as an orphan drug throughout Europe and other countries starting in the early 2000s. It presently remains the only drug specifically indicated for DS in addition to valproate (VPA) and clobazam (CLB) (Brigo and Storti, 2013). This combination showed short-term efficacy in reducing seizure frequency and duration in two double blind, placebo-controlled trials (Chiron et al., 2000; Kassaï et al., 2008) with persistence of its effect on the long range shown by 2 open studies (Thanh et al., 2002; Inoue et al., 2014). Third-generation compounds of many anticonvulsant drugs have been shown to lose efficacy in various chronic epilepsies leading to market withdrawal within their first 3 years (Wong et al., 1999). By contrast, STP efficacy was maintained at a median follow-up duration of 13 and 20 months in DS patients in Japan and the United States, respectively (Inoue et al., 2015; Wirrell et al., 2013). In the experience our center, STP efficacy has been documented for 3 years.

We reviewed our series of DS with *SCNIA* mutations in order to precisely and completely document long-term outcomes and seizure response to STP.

2. Methods

We analyzed records of all DS patients with *SCN1A* mutation who had visited our center at least once between January and December 2013, to perform a cross-sectional study. DS was diagnosed according to the International League Against Epilepsy classification scheme (Berg et al., Commission on classification of the ILAE, 2010). The study protocol was approved by an Investigational Research Board/Independent Human Research Ethics Committee and carried out in accordance with Good Clinical Practice guidelines. The study was conducted in accordance with the Declaration of Helsinki 1975, revised Hong Kong 1989. Written informed consent was obtained from the parent(s) or legal guardian(s) and assent from the study patients.

We reviewed the characteristics of each patient's epilepsy (age of onset, seizure type, duration, frequency, awake/sleep prevalence of seizures, and age of last SE), the AEDs and nonpharmacologic treatments each patient used, and the age at which each patient began taking an AED, as well as how old each patient was at last follow-up.

Seizure frequency was assessed on parents' diaries and/or documented by medical staff, covering the last 6 months preceding last visit. We divided the cohort according to the number of "easily recognizable" and countable seizures, (ie, tonic, TC, and clonic) as well as frequency of seizures including daily, weekly (defined as >3/month), monthly (1–3/month), yearly (<1/month), and seizure remission. Seizure remission was defined as freedom from seizures for at least 1 year at last visit. Convulsive SE was defined as a convulsive seizure lasting at least 30 min (using the same definition used by the STICLO trial) (Chiron et al., 2000).

We compared patients who experienced <3 seizures per month with those who presented with >3 seizures per month using a standard two-tailed Student's *t*-test. Significance was achieved for a p-value of <0.05. Comparison was assessed between both groups by age of: seizures onset, treatment onset, STP initiation, and last SE. Also analysed were SCN1A truncated vs nontruncated protein as well as intellectual development and duration of seizures.

Contingency analyses were performed to compare categorical data between the high- and low-frequency seizure groups and the bilateral Fischer exact test was chosen for binary responses; both seizure likelihood and Pearson's tests were used in all other cases.

Mental development was assessed by neuropsychological evaluation using the Wechsler Preschool and Primary Scale of Intelligence III (Wechsler, 2004), the Wechsler Intelligence Scale for Children IV (Wechsler, 2005), or the Brunet-Lézine test (Joose, 2001) according to age. For all the patients the neuropsychological evaluation was performed between 2012 and 2013. If tests were not feasible because of major behavioral problems, assessments were made clinically. Mental delay was considered severe if intellectual or developmental quotient (IQ/DQ) was <40, moderate if between 40 to <50, and mild from 50 to <70. DS patients with an IQ/DQ >70 were considered neuropsychologically normal/borderline.

SCN1A mutations were classified as missense, frameshift, nonsense, splice-site and gene deletion and were further divided into two groups depending on their effect on the protein (truncated vs nontruncated).

3. Results

3.1. Patients

We included 54 patients (32 males, 22 females). The age of seizure onset ranged from 2 to 9 months (average 5 months). Fever was the triggering factor for the first seizure in 82% of patients (n = 44), and convulsive SE was the initial seizure in 50% (n = 27). In our series, 72% of patients (n = 39/54) had at least one episode of SE, which was typically reported before the age of 4 years (n = 29/39). Age at the end of follow-up ranged from 2 years and 4 months to 22 years (mean age: 10 years and 1 month). Most patients had severe (30%; n = 16) or moderate (48%; n = 27) cognitive disability, while mild disability was detected in 16% (n = 7). Four patients (7%) had no cognitive disability; their clinical characteristics are detailed in Table 1. They had received in the past levetiracetam (n = 13, 24.1%), topiramate, ketogenic diet (n = 12, 22.2%), carbamazepine (n = 8, 14.8%), clonazepam (n = 7, 13%), phenobarbital and clobazam (n = 5, 9.2%), vigabatrin and valproate (n = 4, 7.4%), zonisamide and ethosuximide (n = 3, 5.5%), stiripentol and acetazolamide (n = 2, 3.7%).

3.2. Seizures

At the last follow-up, 96% (n = 52) of patients were experiencing ongoing seizures. Only two were in remission; having been seizure-free for over 2 years, the last seizure for these patients occurred at 46 and 60 months of age, respectively. One was on AED triple therapy (VPA, CLB and STP), while the other was on VPA monotherapy after withdrawal of CLB and STP.

Seizures occurred weekly (>3/month, age range 3–22 years, mean age 11 years) in 38% (n = 20/52) and monthly (1–3/month, age range 2–20 years, mean age 9 years) in 40% (n = 21/52), while 21% (n = 11/52) had <1 seizure per month (age range 3–17 years, mean age 9 years). As shown on Fig. 1A, seizure frequency was moderately lower after the age of 12 years than earlier.

Types of seizures varied with 65% being reported as TC (n = 34/52), 25% as clonic (n = 13/52), 11% as focal (n = 6/52), and 13% as atypical absences in (n = 7/52). Three patients presented tonic seizures and one had massive myoclonic jerks. Patients often presented with 2 or more types of seizures (Fig. 1B).

Seizures were usually short, lasting less than 5 min in 96% (n = 50/52) with half of them being <1min duration (n = 24). Only two patients endured seizures longer than 5 min and such long seizures were not reported after the age of 16 years (Fig. 1C).